FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

+ + + + +

5120 '01 MAY 17 A11:23

ARTHRITIS ADVISORY COMMITTEE

+ + + + +

MEETING

+ + + + +

THURSDAY
APRIL 19, 2001

+ + + + +

The Advisory Committee met at 8:00 a.m. in the CDER Advisory Committee Conference Room, 5630 Fishers Lane, Room 1066, Rockville, Maryland, Dr. E. Nigel Harris, Acting Chair, presiding.

PRESENT:

E. NIGEL HARRIS, M.D.	Acting Chairman
JENNIFER ANDERSON, PhD	Member
KENNETH D. BRANDT, M.D.	Member
LEIGH F. CALLAHAN, PhD	Member
JANET D. ELASHOFF, PhD	Member
PAMELA J. FIELDS	Guest
GARY S. FIRESTEIN, M.D.	Member
JACK KLIPPEL, M.D.	Guest
MATTHEW H. LIANG, M.D., MPH	Consultant
WENDY W. McBRAIR, RN, MS, CHES	Consumer Rep
YVONNE S. SHERRER, M.D.	Member
EARL D. SILVERMAN, M.D.	Consultant
BARBARA C. TILLEY, PhD	Consultant
H. JAMES WILLIAMS, JR., M.D.	Member
KATHLEEN REEDY, RDH, MS	Executive Secretary

This transcript has not been edited or corrected, but appears as received from the commercial transcribing service; the Food and Drug Administration makes no representation as to its accuracy.

I-N-D-E-X

P-R-O-C-E-E-D-I-N-G-S

(8:17 a.m.)

DR. FIRESTEIN: If the committee members could please take their seats, we'll go ahead and get started.

I am Gary Firestein. Everybody, welcome today. I am the "Acting" Acting Chair, which means I'm far down on the totem pole, I suppose. In order to get started, why don't we begin by having the members of the Committee introduce themselves, going around the table, beginning on my right.

MS. FIELDS: Pam Fields. I'm from the Arthritis Foundation in Cincinnati, Ohio, and I'm here as a patient.

DR. KLIPPEL: Hi, I'm Jack Klippel. I'm a rheumatologist, and I, too, am with the Arthritis Foundation.

DR. LIANG: Matthew Liang. I'm a general internist and rheumatologist from Boston.

DR. SILVERMAN: Earl Silverman, a pediatric rheumatologist from Toronto.

MS. McBRAIR: Wendy McBrair, Director of the Southern New Jersey Regional Arthritis Center, and I'm here as the consumer rep.

DR. WILLIAMS: James Williams. I'm a

rheumatologist from Salt Lake City.

DR. SHERRER: Yvonne Sherrer. I'm a rheumatologist from Ft. Lauderdale.

DR. FIRESTEIN: I'm still Gary Firestein from San Diego.

MS. REEDY: Kathleen Reedy, Executive Secretary of the Arthritis Advisory Committee.

DR. CALLAHAN: I'm Leigh Callahan. I'm a epidemiologist and outcomes researcher from the University of North Carolina in Chapel Hill.

DR. BRANDT: Ken Brandt. I'm a rheumatologist from Indiana University.

DR. ANDERSON: Jennifer Anderson. I'm a statistician from Boston University Medical Center.

DR. ELASHOFF: Janet Elashoff, biostatistician, Cedars-Sinai and UCLA.

DR. TILLEY: Barbara Tilley, biostatistician, Medical University of South Carolina, technically inefficient.

DR. JOHNSON: Kent Johnson, rheumatologist, RDA.

DR. GOLDKIND: Larry Goldkind, Medical Team Leader, FDA.

DR. BULL: Jonca Bull, the Acting Division Director and Deputy Office Director.

DR. FIRESTEIN: Okay, thank you very much.

We will -- Do you want to say a word? Then we'll begin, actually, with the meeting statement from Kathleen Reedy.

MS. REEDY: The conflict of interest statement for the Arthritis Advisory Committee open session on April 19, 2001: The following announcement addresses the issue of conflict of interest with regard to this meeting, and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the Committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting.

With respect to FDA's invited guests, Dr. Jack Klippel has reported an interest which we believe should be made public to allow the participants to objectively evaluate his comments. Dr. Klippel would like to disclose that he consulted with Genelabs ten years ago to offer advice about trial design in systemic lupus erythematosus.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask, in the interest of fairness, that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

DR. FIRESTEIN: Thank you. And we will begin the meeting with the welcome and introduction from Dr. Jonca Bull.

DR. BULL: Good morning. First, welcome to this Advisory Committee meeting. A special welcome to our Advisory Committee members, interested guests, and to the sponsor.

I would like to also extend a thank you to our Advisory Committee members who have taken time from very busy schedules to share their talents and expertise with us today.

We are here today to discuss New Drug Application NDA 21-239 for GL701 by Genelabs Technologies. It is here to be discussed for the indication of the improvement of disease activity

and/or its symptoms in women with mild to moderate systemic lupus erythematosus and the reduction or corticosteroid requirements in women with mild to moderate SLE.

The IND dates back to December of 1993. Orphan drug designation was granted in July of 1994, and in March 1999 fast track drug designation was granted by the Division on the basis that SLE is considered a serious disease for which no adequate therapy is currently available, noting that there have been promising but inconclusive results from clinical investigations thus far.

The issues to be addressed by the Committee in today's meeting will provide important additional perspectives to the agency on the safety and efficacy of GL701 in the treatment of patients afflicted with SLE.

The Division's decision to bring this application to this Advisory Committee reflects our concern that these study results be given wider expert review and discussion in order to more fully evaluate the current application and further consider the many complexities associated with the study of this serious disease. Thank you.

DR. FIRESTEIN: Thank you very much. Next

the regulatory background will be presented by Dr. Kent Johnson.

DR. JOHNSON: Thank you very much, Mr. Chairman. I have about five or ten minutes of introductory remarks, a little bit about the background regarding lupus itself and a little bit about the regulatory background for this submission.

A lot of this is not going to be new to anybody in the audience here, but I thought it would set sort of the scientific backdrop. We, obviously, have a challenging charge for discussion today with a disease of this type, which is really quite multi-factorial and has quite a variable short and long term time course, and it has this peculiar mixture of -- or at least relatively peculiar mixture of pathology with the disease and the drug toxicities being kind of mixed together, making assessment more difficult.

We will talk a bit about disease -- I'm going to mention a few -- show a few slides about disease activity indices this morning. Some of these played a dominant role in the clinical trials that we will talk about today, and finally the whole role of the facility. The pros and cons of short and long term steroid use in lupus is another one of the dominant background themes here.

When one thinks about lupus clinical trials, you obviously need an assessment measure. There has been a number of these advocated over the years. Some of the people in this room have been instrumental in developing these measurements.

The SLEDAI and the SLAM played an important role in the trials. We'll talk about the BILAG and the ECLAM, and there's a few others also that I'll mention just briefly.

There has been some work. We need to move much more -- much further ahead, I think, in this regard, but there has been some work with thinking about how to construe assessment in the setting of an RCT.

OMERACT started some work in defining various domains here, and this article by Dr. Strand at the bottom is a nice review of the instruments and their characteristics.

The SLEDAI, just briefly -- you'll hear a lot more about this today -- was derived by a Delphi process of physicians and statisticians. It is not a change measure. It is a static measure that captures the previous ten-day time frame.

It has 24 components that are weighted in various ways, one, two, four and eight, and does not

cover specifically fatigue or steroid use. Here are the components of the SLEDAI. The findings across in the top group here are weighted 8, and then some of the less severe manifestations are four and two and one, and you simply add these all up.

The SLAM was developed in Boston in the late 1990s by Dr. Liang and his colleagues and involved a judgment concerning many of the -- there's a typo there, I'm sorry -- many of the ACR features of lupus that were in their 1982 definition of lupus.

It also had a patient and a physician global. This, too, is a static measure that captures a time frame over the previous month and is composed of 24 clinical, seven laboratory measures and the two globals. These, too, are weighted by a one to four -- They are weighted in four categories that vary from absent to severe.

There are three constitutional symptoms, four skin symptoms, three eye symptoms, and you can go through all these, and these are the constituents of the SLAM measurement.

I just wanted to show one slide on each of two other measures, just to give you a flavor of the different ways that you can construct measurements for a complex disease like this.

This is the British BILAG system, which was driven by a number of consensus meetings. The key question here was so called intent to treat. I don't mean that in the clinical trial sense, but in the sense of when you have reached a threshold to change treatment, to institute a major change in treatment, which was defined as substantial dose steroids or immunosuppressives.

So this is a transition measure. It is not a static measure, unlike the previous two. There are four states that could be thought about, the top one being, as I mentioned, the need for adding high dose steroids of immunosuppressives, and eight organ systems were assessed in this measurement. Again, they were weighted with a 9, 4, 1 and zero scale.

Finally, there is another system that was developed across Europe from a database. This was a collection of 700-odd patients from 14 countries that then was put in a database and optimized statistically in order to ascertain what was the most optimal measure that would reflect this database, again a static measure with a time frame of one to three months.

Finally, I don't comment at all on the performance characteristics. There is a large

literature of performance characteristics of these various instruments, mainly from observational studies. The content of so called validation is various defined, but this is one standard approach to it. OMERACT has had some comments about this, too, with their OMERACT filter which is constituted by truth, discrimination and feasibility.

What we are missing here is any substantial contribution from controlled clinical trials, which is what you really want in order to help you better design a trial, either from previous clinical trials or from pilot studies when you are thinking about what instrument to use to assess disease in a clinical trial.

Here's a few trials that I think everybody in this room are probably aware of, but just for review. Recent RCTs in mild to moderate lupus, not the lupus nephritis heritage that everybody is aware of.

This is the Canadian Rheumatology Association hydroxychloroquine withdrawal trial that was published in '91, a six-month study that used a survival analysis with the endpoint being time to clinical flare or severe exacerbation.

The CSSRD trial which was published in '94

was a standard comparison of means to assess a variety of endpoints. This was a one-year trial.

Finally, there was reported in JRheum in '99 a 41-patient, six-month trial of methotrexate versus placebo, which did use the SLEDAI and the pian VAS in prednisone use as primary endpoints.

It is of concern sometimes when you have more assessment measures than you do clinical trials, and I think that is where we stand in lupus right now.

There have been some pilot studies that you are aware of. I think these are in both my document and the sponsor's document. Specifically, there was a very interesting publication in '95 by the Stanford group that was really the pilot study for this program that used the SLEDAI and the globals in prednisone dose as the endpoints, a three-month 28 patient study.

Dr. van Vollenhoven did a similar -- did another study, a six-month study in severe lupus patients which also, I thought, was very interesting, enrolling patients who had protocol-specified criteria for nephritis or hematologic disease or serositis with an endpoint that was, I thought, nicely described as a stabilization of those features.

Finally, there is a large Taiwan study

that I touched on in my review and that the company will tell us more about today that used a change in the SLAM at the six-month point as the endpoint, and then there is a small, ongoing study in male lupus.

One final slide regarding the early discussions that the agency and Genelabs had. This goes back many years, you know, back to '93-94. We will be talking about two primary studies in this particular NDA. They are called 94-01 and 95-02.

The first one is a three-arm -- They are both placebo controlled. The first one has two doses, a three-arm study, about 60 patients per arm. The second one is about 190 patients per arm, two-arm study.

The first one is driven by the concept of trying to demonstrate steroid sparing. There were a lot of discussions that surrounded this topic, and there was really quite broad consensus that genuine steroid sparing would be a meaningful contribution to the clinical situation with lupus patients and, therefore, should carry evidentiary weight in an NDA.

The other design seen for both these studies was an attempt to try to capture on a by-patient basis what happens as a consequence of the trial.

There are statistical arguments pro and con for these sorts of approaches, and there is some argument that you may lose information if you collapse it together and make a judgment about a patient, whether it's a pro and con judgment or a grade of one, two, three or whatever. But by-patient assessments were thought to at least get a lot of the debate about the interpretation of the trial up front in the design stage as opposed to in the analysis stage.

In addition, I think there was a lot of sympathy on the part of -- There was a lot of sympathy that these sort of things are much more clinically intuitive to the patient and the doc.

Finally, there were discussions that were always int he backdrop of what would be a sufficient safety database for a maneuver of this type.

So that said, I'll turn the floor back to the Chair, and we will move on with the sponsor presentations.

DR. FIRESTEIN: Thank you very much. Now we have time scheduled for the Genelabs representatives to make their presentations.

I would ask the members of the Committee, if possible, to please hold questions until the end of the presentation, and then that primarily for

clarification. There will be time later on for an extensive discussion and question and answer period. Thank you.

DR. GURWITH: Hello. I am Marc Gurwith, the head of drug development at Genelabs, and I am just going to provide a brief introduction. Go to the next slide.

This is our outline of our presentation. Bob Lahita from New York Medical College will give you some background and rationale for the use of our product, GL701, in lupus, to be followed by Michelle Petri from Johns Hopkins University who will present the efficacy data from our studies, followed by Frank Hurley from Quintiles, and then provide a statistical assessment of the efficacy findings. Then Michelle will continue with a presentation of safety, and then finally, Murray Urowitz from University of Toronto will provide a clinical perspective on our clinical trials and the potential role of GL701. Next slide.

In addition, we have some consultants in the audience with us: Allan Tall from Columbia University; Bill Kramer, locally, for pharmacokinetics; Michael Madaio from University of Pennsylvania; Vibeke Strand from Stanford; Sam Yen from University of California at San Diego; and then

finally Ron van Vollenhoven has joined us from Karolinska. Next slide.

Just very briefly in terms of nomenclature, our product is GL701 or DHEA. But in fact, the USAN or generic designation for DHEA when it is a synthetic drug is prasterone. Basically, prasterone is a synthetic equivalent of DHEA or dehydroepiandrosterone, the endogenous hormone.

We have chosen to refer to it as GL701 throughout our presentation, mainly because that is what was used -- That's the code we used during our clinical trials. Most people are not yet familiar with the term prasterone. Next slide.

Then finally, Jonca Bull read these already, but we are here to discuss two indications, one for improving disease in women with lupus and the second, helping women reduce their corticosteroids, and again with mild to moderate lupus.

So now Bob Lahita will give you some rationale and background.

DR. LAHITA: Good morning, members of the Committee and distinguished guests. It's a great pleasure to be here to present the background on this interesting compound. Next slide.

As we all know and we have heard from Dr.

Johnson, systemic lupus erythematosus is a very, very important illness. It is an inflammatory, multi-system, autoimmune disease for which the etiology is not known, and the treatment at best is really modest.

The morbidity of the disease is very, very important to our patients. There is disease associated morbidity, which I will show you in a moment, and there is also treatment associated morbidity, not the least of which is corticosteroid associated morbidity, which can be as high as 89 percent from published works.

The mortality within this disease itself, which affects largely women and after puberty, the ratio of women to men ranges from ten women to 15 women for every male that has the disease. It's about five to ten percent at ten years.

Early in the disease, there is activity which is organ destructive. There are all sorts of nondescript complaints from patients which are probably based in immunologic phenomena that we know little about. Infections are extremely important.

In late disease and now the most common cause of death within the illness is atherosclerosis. Next slide.

If you look at the damage within lupus

from this particular slide, which is a compilation of damage index domains from the systemic lupus international cooperating clinics and the American College of Rheumatology, we could say safety that 50 percent or more of patients have one or many or more of these damage indexes.

The most striking is at the top of the slide, which shows you the musculoskeletal complaints being the highest, at approximately 22 percent. We go downwards from there to neuropsychiatric, renal, ocular, all the way down to two percent of patients having premature gonadal failure.

This is only the tip of the iceberg, as we would say. Next slide.

Now there's a lot of rationale behind the use of an androgen, a weak androgen in particular, in the treatment of this disease, systemic lupus. The rationale really goes back way before 1985, as is seen on this particular slide, to the early Seventies where a number of studies commenced in mice, mice that, of course, are different than humans because of inherent genetic defects, and all, of course, members of the mouse strains that come to lupus eventually.

It was very peculiar that in several strains, one of which is listed here on the slide, the

nzb/nzw F1 murine model, that there is 100 percent mortality at ten months in the females of the strain, very much a female skew like one would expect to see in the human sporadic disease.

The mortality within that strain was reduced significantly by removing the ovaries from the females of the strain, thereby prolonging life, or in fact, injecting androgen or putting Silastic implants in these female mice with androgens would prolong life and decrease morbidity considerably.

Conversely, the males of the strain, if one were to do an orchidectomy and inject estrogen into such animals, you would accelerate the morbidity and mortality.

Then about 1985 in early studies of Lucas, et al., it was noted that dehydroepiandrosterone, when given to these mice in Silastic implants or injected, would in fact decrease the mortality and morbidity within this particular strain of mice.

The in vitro studies then explored the biological mechanisms behind the use of androgens. And, of course, DHEA being a weak androgen was the optimal drug for the treatment of these animals.

The altered cytokine profiles that were seen with DHEA in the murine model were quite

interesting. Cytokines such as interleukin-6 were depleted, as well as IL-4 ad IL-5, representing the TH2 helper cell or anti-inflammatory cytokine numbers. They were decreased, whereas the inflammatory TH1 type cytokines were increased. The IL-2, for example, in these animals were noted to be increased. Next slide.

So in essence, using the paradigm, which is probably too simplistic, of TH1 being associated not with lupus but with diseases like rheumatoid arthritis and multiple sclerosis, and the TH2 cytokines being associated with lupus, use of the DHEA in the animals was able to shift the cytokine profile away from the anti-inflammatory to the pro-inflammatory cytokine profile.

Now the clinical rationale of dehydroepiandrosterone in humans was based, of course, in the sex distribution which, as I mentioned, is about 90 percent female and ten percent male after pubescence. Low levels of DHEA and other androgens in women with SLE were discovered in our laboratory and other laboratories, and this was not only DHEA but DHEA sulphate, androstenedione and, of course, free testosterone.

The reasons for the depletion of androgens in women with this disease still remains unknown, but

one interesting aspect of this was that oxidation of the androgens, particularly testosterone at C17, was accelerated, and the acceleration was seen largely in women. It doesn't occur in males, perhaps because of the large component of testosterone which comes from the testicles.

DHEA and testosterone further suppressed -- were further suppressed by corticosteroid use, and that has been an ongoing observation that may or may not have importance within the disease lupus itself, for various systems like cognition etcetera.

Now it also known, as I discussed in the murine model, that IL-2 levels are suppressed in systemic lupus, and there is adequate data to show that in vitro that DHEA increases IL-2 production by T lymphocytes. And there is also other data to show that IL-2 is depleted in the human with systemic lupus erythematosus, in contradistinction to the patients with rheumatoid arthritis, I might add.

Then at the lower end of this slide you see that DHEA inhibits IL-6 secretion from mononuclear cells. This, of course, mirrors that which is seen in the murine model where I already said that IL-4, 5 and 6 TH2 cytokines are depleted in the mouse model. Next slide.

This slide shows you the interesting fact that DHEA sulphate and testosterone levels are depressed in the presence of prednisone or any corticosteroid, for that matter, that baseline DHEA sulphate in the absence of prednisone is at one level and as soon as the prednisone is added, these DHEA sulphate levels are depleted.

The baseline testosterone also drops in the presence of prednisone, and this is, of course, the case for every androgen. So that when we did the original radioimmunoassay studies of the women that were studied for androgens, plasma androgen levels, we were very careful to avoid patients who had been on corticosteroids. Next slide.

So the rationale, in summary, for the use of androgen therapy in the disease systemic lupus erythematosus is clear. Some of the reasons for the metabolic abnormalities are not very clear.

There are two reasons, two rationales. First is endocrinologic. That is that there are extremely low androgen levels in women with systemic lupus and, secondly, that there is higher oxidation of testosterone at C17 in women with lupus. The reasons for that are unknown.

Secondly is the immunologic basis, that

there is a decrease of interleukin-4, 5 and 6 or the TH2 cytokines, and an increase of IL2, and that's a typo on the slide. That should be TH1 cytokines, and also there are other phenomena that we have observed in mice such as increased cytotoxicity and change of natural killer cell activity, etcetera. Next slide.

Now it's my great pleasure now to introduce you to Dr. Michelle Petri.

DR. PETRI: Good morning, Dr. Harris, members of the Committee and guests. As Dr. Johnson told you, the first trial of DHEA for lupus was done at Stanford University. It was a double blind, placebo controlled trial in 28 women followed for three months.

In this study there was improvement or stabilization in the SLEDAI index and in the Physician Visual Analog Scale. In addition, the patient VAS improved significantly, and the number of flares decreased, almost achieving statistical significance. Finally, there was a decrease in prednisone requirements.

These promising findings held true in an open-label study that followed. These results, you will hear this morning, have now been confirmed by Genelabs in trials of larger patients for longer

duration. Next.

Because the FDA does not have a guidance document for lupus clinical trials, the clinical trial design process you will hear about this morning was very much a collaboration between the FDA, Genelabs and multiple lupus consultants.

There were two very pertinent Arthritis Advisory Committee meetings, one in 1995 in which the two efficacy per-patient endpoints were discussed, corticosteroid reduction and improvement in disease activity, and the 1999 Arthritis Advisory Committee meeting in which we discussed clinical trial endpoints for lupus. Next.

As you have heard, lupus patients carry a tremendous burden of disease. Most patients have patterns of flares or continuously active disease. Flares continue to occur even in patients who have long established lupus.

You heard from Dr. Lahita that the morbidity is a very important issue, and the damage that happens in our lupus patients it not just from lupus itself, but the prednisone treatment contributes in a major way.

You are not surprised to hear that the quality of life of lupus patients is very poor, on the

par with patients who are HIV infected. Next.

Both the systemic lupus international collaborating clinics and OMERACT have agreed that randomized clinical trials in lupus need to both measure and report the three clinical domains of lupus.

First, of course, is disease activity. In the studies you will hear about today, two measures were used, the SLEDAI and the SLAM. To measure organ damage, a clinical deterioration index was used that was made in collaboration with the FDA. It measures very similar things to the SLICC Damage Index.

Finally, what is most important to our patients is quality of life. In the trials done by Genelabs the Krupp Fatigue Severity Scale and the patient VAS were used, but the SF-36 was measured as well. Next.

You have heard that there are two efficacy endpoints for these clinical trials. The first is reduction in corticosteroid requirements. If the SLEDAI was stable or improved, an algorithm dictated steroid taper in that trial.

The second is improvement or stabilization in lupus. This was a very stringent outcome. It was based on improvement or stabilization in each of these

measures, the SLEDAI, SLAM, Krupp Fatigue and Patient VAS, without any clinical deterioration. Next.

I'll be describing to you the GL701 development process. There are two prospective randomized clinical trials for efficacy. The first is 94-01 for corticosteroid reduction. The second is 95-02 for improvement in lupus.

There is a very similar improvement trial done in Taiwan. There is also a long term open label safety study and, finally, as Dr. Johnson mentioned to you, there is a male lupus study, but it is ongoing, and it is still blinded. So no data can be presented from that study. Next.

The first study, 94-01, had as its objective reduction in corticosteroid requirements. Next.

This is a double-blind, randomized, controlled clinical trial with three arms, 100 and 200 milligrams of GL701 versus placebo. Patients were dosed from seven to nine months with monthly assessments. The prednisone dose was reduced at each visit if the SLEDAI was stable or improved, based on the algorithm I mentioned to you. Next.

To enter this trial, women had to be on a stable prednisone dose of 10-30 milligrams a day, and

steroid dependence had to be demonstrated either by an unsuccessful prednisone taper or, if there had not been any taper, this dose had to have been stable for 12 weeks. Next.

Now the responder or the efficacy endpoint here is sustained prednisone reduction. This means the prednisone must be decreased to less than or equal to 7.5 milligrams per day for more or equal to two months, and the last visit must be included. Next.

At baseline the three arms in this trial were balanced in terms of age, race, and menopausal status. Next.

The baseline characteristics are also balanced between the arms in terms of treatments, prednisone and antimalarial use, in terms of the baseline SLEDAI, and also in terms of the baseline DHEA-S. This mean in the 200 milligram group is elevated because of three outliers. As you can see, the medians are similar. Next.

One of the questions you will be asked to discuss this afternoon is the impact of the baseline SLEDAI in this trial. At a pre-study investigator meeting there was concern about whether patients with zero or low SLEDAI scores should be enrolled in this trial.

We didn't know whether patients with these low scores had smoldering disease that was going to flare as we tapered the prednisone or whether they had inactive disease that was, in fact, not steroid dependent.

Because we did not know, to address this a blinded analysis was done without any treatment group attribution, and was reviewed prior to study unblinding. Next.

These are the results of that blinded analysis. As you can see, the patients with the zero to 1 to 2 SLEDAI scores have a different response rate. They are a different population, suggesting that they aren't as steroid dependent. Next.

After the study was completed, we could actually go and look at their clinical characteristics. Of those patients with the low scores, 51 percent had zero, no measurable activity by this index. Thirty-eight percent had achieved a score of 2, but it was due to serologies, a low complement or a high anti-DNA.

The rheumatologists on the Committee know that serologies alone do not mean active clinical lupus, and most rheumatologists do not treat serologies alone. Therefore, this group of patients

with SLEDAI scores of zero to 2 differed in their clinical characteristics, not just in terms of their response. Next.

So these data suggest that the baseline SLEDAI group greater than 2, a more active disease group, represents a different population and, for this reason, Genelabs defined these patients as a subgroup prior to unblinding.

Now this really is no different from what we do in rheumatoid arthritis, for example, where we define what an active patient is to belong in a trial. Next.

About three-fourths of the patients completed this trial in all arms, and there is no pattern in terms of the primary reasons for withdrawal. Next.

This is the most important slide for this study. These are the responders. If we look at all patients, 55 percent on the 200 milligram dose of GL701 were responders, as opposed to 41 percent in the placebo group. The P value is 0.110, suggestive of a strong trend.

If we look at the patients with more active lupus, those patients whose SLEDAI scores are greater than 2, 51 percent in the 200 milligram dose

are responders, as opposed to 29 percent in the placebo group, with a P value of 0.031. Next.

You can see on this slide the response rates divided up by the baseline SLEDAI score. The important conclusion is that the 200 milligram dose of GL701 maintains its efficacy even at the higher SLEDAI baseline scores. Next.

There was a mild but statistically significant difference in the baseline prednisone dose for the SLEDAI greater than 2 group between the 200 milligram arm and placebo. Therefore, we looked at the patient who started out with a baseline prednisone dose of 10-15 milligrams and those who started out greater than 15-30 milligrams.

As you can see, we see the same pattern of response, highest at the 200 milligram dose, much higher than placebo. The same thing is true for the 15-30 milligram baseline prednisone. Next.

You are going to be asked to address in one of the questions whether it should be a prerequisite to show mean prednisone reduction at the last visit before you accept the conclusion of sustained prednisone reduction for two or more months, including the last visit.

As you can see from the analysis of mean

prednisone reduction at the last visit, there did not appear to be any difference between GL701 or placebo. Dr. Hurley is going to tell you more about this in his statistical presentation. Several outliers turn out to affect this.

What I want to talk to you about is the clinical issue. This endpoint does not fully reflect prednisone reduction for two reasons. The first is there was no algorithm for prednisone increases. Secondly, this analysis only reflects prednisone reduction at the last day.

What matters to clinicians and to patients is whether their prednisone stays down for a longer time during the trial. Next.

I want to show you an example of the problem of not having an algorithm for prednisone increases. Here is a patient in the trial whose SLEDAI is going down and, as the SLEDAI goes down or stays stable, the algorithm dictates a reduction in her prednisone dose, as you can see here.

At the fourth visit her SLEDAI went up. So the prednisone was stable. Now you see that the SLEDAI is remaining perfectly stable. There is a reduction here, but look at what happens at month six. All of a sudden, the prednisone jumps up higher than

it was at baseline.

Have the SLEDAI missed some disease activity? Was this patient having a bad flare? No. The comments on this patient indicate this patient was perfectly stable. An outside physician saw the patient and suddenly increased the prednisone. This was not the investigator. So you can understand, there is a problem in not having an algorithm for prednisone increases. Next.

For this reason, we think this is a much more informative analysis. Let's look at the number of days that the patient stayed at a prednisone dose of less than or equal to 7.5 milligrams per day, in other words, physiological dose.

If we look at all patients, you can see that at the 200 milligram dose the mean and median days is substantially higher than with placebo, a P value of .069. If we look at the patients with more active lupus, this is even more dramatic with a P value of .013 or .015. Next.

To summarize the efficacy shown in this first trial for corticosteroid reduction, looking at all patients for the major endpoint, sustained corticosteroid reduction, it occurred in 55 percent on 200 milligrams, 41 percent on placebo, with a P value

indicative of a strong trend.

If we look at the number of days where prednisone was less or equal to 7.5 milligrams, obviously, it was in favor of 200 milligrams with a P value of .069. Looking at the population with more active lupus, the higher response rate with 200 milligrams met statistical significance. The greater number of days that the prednisone was at or below 7.5 milligrams also met statistical significance, and there was a dose response for trend, 200 versus 100 versus placebo .033. Next.

The second study I will be telling you about is 95-02. This study had as its objective improvement or stabilization in lupus. Next.

This is also a double-blind, randomized, parallel design trial, duration 12 months with assessment every 90 days. Only two arms, 200 milligrams versus placebo. If a patient was taking prednisone, immunosuppressives and antimalarials at baseline, they continued unchange throughout the trial.

At eight sites, DEXA scans for bone mineral density were performed on patients who had been on chronic corticosteroids for six months prior to the study and, of course, throughout the study.

This is a very important endpoint because, as you heard from Dr. Lahita, corticosteroid associated osteoporosis is one of the most frequent forms of damage in SLE patients. Next.

To enter this trial, the women had to have had a SLAM score greater than or equal to 7, a prednisone dose was less than or equal to 10 milligrams. Now based on what you have already heard from study 9401, there was an evidence based protocol amendment to require more active lupus at baseline, and for this reason enrollment was increased to capture more of these patients. Next.

The primary endpoint here is a responder, defined as follows: There had to have been improvement or stabilization in each of the following: Two disease activity measures, SLEDAI and SLAM; two constitutional measures, the patient VAS and the Krupp Fatigue Severity Scale.

This was based on the mean of the on-treatment visits, compared to the mean at baseline, and no clinical deterioration. Next.

Clinical deterioration was defined as new or progressive organ disease, serious drug toxicity, or new or increased dose of prednisone or immunosuppressive drugs. Next.

You will be asked to comment in one of the questions this afternoon on the development of the analysis plan. You know that there are no guidelines for lupus clinical trials. This is very much a collaborative process between Genelabs, the FDA and multiple consultants, and it was a learning process.

Two additional key issues were identified from the inception of the study to completion of the final analysis plan. One is to define stabilization for each of the instruments used in the responder definition. We have nicknamed this the "window concept." The other is to identify the primary analysis dataset. Next.

First, let's discuss stabilization for each instrument, the idea of a window. Everyone here knows that, when we do rheumatoid arthritis trials or virtually any trial in rheumatology, we have two baseline pre-treatment evaluations of disease activity. Why? Because all of our measures and instruments have inherent variability.

This is certainly true in these lupus trials. We knew that there was test/retest variability. This has been published by Dr. Liang and many other groups, including my own.

Therefore, it was necessary to define what

stabilization meant in each of the instruments. This was not finalized prior to initiating this study. Next.

Genelabs pre-defined the window in October 1998 before study completion unblinding. The pre-defined window was .05 for the SLEDAI and the Krupp Fatigue Severity Scale, one for SLAM, and 10 for the patient VAS.

Now after the study was completed, data was available to obtain an evidence based window. Why? Because there were two baseline measures, and we could actually look at those two baseline measures to see what the variability actually as.

So for SLEDAI the mean change was .57; for SLAM, .71; for the patient VAS, 11.4; and for Krupp Fatigue .54. You can see that this evidence based analysis of variability agrees very nicely with the pre-defined window.

Now the robustness of this concept of the window will be further discussed by Dr. Hurley in the statistical section. Next slide.

I wanted to show you how clinically intuitive this is. Here is an example of a patient who would have been classified as a nonresponder if no window had been used. When a window is employed, she

is a responder. Now see if you agree.

During the trial her SLEDAI improved. Her patient VAS improved dramatically. Her SLAM improved substantially. Now her mean on-treatment Krupp Fatigue worsened by .01.

Now you all, I am sure, agree with me that that's a minimal deterioration. This lady is stable on the Krupp Fatigue. The window allows us to call these minimal changes still being stable. Next.

There are several secondary endpoints in this trial: Mean changes in the four instruments that made up the responder definition; bone mineral density in the patients on chronic corticosteroids; and the proportion of patients with a lupus flare. Next.

The baseline demographics in the all randomized group, the intent to treat population, is balanced in terms of age, race, and menopausal status. Next.

The baseline characteristics in the all randomized population are also balanced for the four instruments that make up the responder definition for treatments, prednisone, antimalarial use and immunosuppressive drugs and for the baseline DHEA-S levels. Next.

In this study 66 to 74 percent of the

patients completed the trial. There were more dropouts in the 200 milligram arm, because of adverse events. Next.

If we look at the patient response in the intent to treat population, there was only a slight benefit from being on GL701, but what we care about are the patients with more active disease. You can see in that population the response rate was 59 percent for GL701 versus 45 percent on placebo with a P value of .017. Next.

Now remember that you will be asked to discuss this this afternoon, the appropriate population for analysis. The original protocol that Genelabs submitted before starting the trial specified intent to treat.

In an intent to treat analysis, a patient who does not have any post-baseline measures is classified as a nonresponder. This potentially dilutes out a positive treatment effect.

Genelabs had discussed an analysis plan since February of 1995 and submitted their analysis plan before the study was completed and unblinded. Their analysis plan specified a per-protocol population.

Now how is this defined? Patients treated

for greater than or equal to 60 days who had at least one post-baseline assessment beyond 60 days. Please remember that the first scheduled assessment was at 90 days.

Some patients excluded from this protocol include 32 patients who had no post-baseline measures, one placebo patient who was a major protocol violator, and two placebo patients who had less than 60 days of treatment.

The per-protocol population is virtually identical to a modified intent to treat. In a modified intent to treat, if a patient does not have any post-baseline measures, she is excluded. There is only a three-patient difference, these three patients. Dr. Hurley will tell you that there is no major difference in the analyses if we do a per-protocol population or a modified intent to treat. Next.

We want to address one of the issues you will be discussing this afternoon: Does using a per-protocol population introduce any bias?

There are comments on the reasons why patients withdrew and, therefore, were excluded from the per-protocol population. These comments were read to me in a blinded fashion, and I then classified the reason into one of these four boxes: Possibly related

adverse events, lack of efficacy, unrelated to safety or efficacy, or no information.

As you can see, there appears to be excellent balance between the GL701 and placebo patients in these boxes. This appears to be random. The null hypothesis is not voided. Next.

An additional way to look for potential bias in the excluded patients from the per-protocol analysis is simply to compare their baseline characteristics.

As you can see, the excluded patients are virtually identical to the per-protocol patients in terms of the four instruments that make up the responder definition, age and prednisone dose. Next.

This is the most important slide for study 95-02. This is the percent responders of the per-protocol population. As you can see, 58 percent were responders on 200 milligrams versus 46 percent on placebo. The P value is .018.

Looking at the patients with more active lupus, it is 66 percent versus 49 percent with a P value of .005. Next.

As in 94-01, the efficacy of GL701 is maintained even at the higher baseline SLEDAI scores. Look at how impressive it is for patients who had

baseline SLEDAI scores of 8 to 12. Next.

Now for this study as well, one of your questions this afternoon asks you to address the use of the population SLEDAI greater than 2, the patients with more active lupus. In 94-01 I showed you that most of the patients with low SLEDAI scores did not appear to have active disease.

The same thing is true in 95-02. Forty-three percent of these patients had a score of zero. So no activity could be demonstrated using this index. 28 percent had only had points accrued because of abnormal serologies. So 71 percent of the patients with scores of zero, one and two had no evidence of clinical activity using the SLEDAI instrument. Next.

I would now like to turn to the secondary efficacy outcomes in this trial, and the first is mean changes in the four scoring instruments that made up the responder definition.

As you can see, the patients on GL701 won on all of these, but it's especially impressive how much improvement they had on the patient VAS, almost reaching statistical significance. Next.

While this trial was underway, the SELENA study, the safety of estrogen in lupus national assessment study, through a collaborative developed a

definition of flare. Genelabs then adapted that definition for this study.

So flare was defined as an increase in corticosteroids, hospitalization for lupus, new or increased use of immunosuppressives, or clinical worsening. Next.

As you can see, the patients on GL701 had fewer flares, both in terms of the per-protocol population and the patients with more active lupus, but this did not reach statistical significance. Next.

The bone mineral density substudy was done at eight different sites in patients who were on chronic corticosteroids. As you can see, there is good balance between the placebo and GL701 patients with some slight differences in that more placebo patients were taking estrogen and Alendronate, and more GL701 patients were taking calcitonin. Next.

The results in bone mineral density are especially striking. The GL701 group had substantially better bone mineral density in the lumbar spine. In fact, corticosteroid associated osteoporosis was most pronounced in the lumbar spine.

You can see that there was also a major difference in the hip, although at the hip it didn't

quite reach statistical significance. Next.

I think this is a very instructive analysis. It lets you look at the patients who had greater than a three percent gain in their bone mineral density or greater than a three percent loss. You can see that the GL701 patients were much more likely to gain three percent in both the lumbar spine and the hip.

Look what happened to the placebo patients. About a third lost more than three percent of their bone mineral density in the lumbar spine during this one-year study. Next.

Now to summarize the efficacy information from 95-02, the improvement stabilization study, using the intent to treat population, the more active lupus group, SLEDAI greater than 2 had a higher response rate with GL701 than with placebo, with a P value of .017.

Using the per-protocol population, again there is a higher responder rate with GL701 with a P value of .018. If we look at the more active lupus population, the P value is .005.

In terms of the secondary efficacy outcomes, improved bone mineral density is especially striking in the lumbar spine with a P value of .004.

Patient global assessment improved. Remember, that was also shown in the Stanford trial. Flares were reduced, as again shown in the Stanford trial. Next.

Now I would like to move to a very similar study on improvement stabilization of lupus that was done in Taiwan. It was a double-blind, randomized clinical trial, same objective as 95-02.

Women with active lupus were enrolled, baseline SLAM score greater than or equal to 7, and again there was the evidence based amendment to require enrollment of women with more active lupus, defined as SLEDAI score greater than 2, two arms, 200 milligrams versus placebo. This is a six-month study as opposed to the 12-month duration in the U.S. study. Next.

The baseline characteristics were balanced between placebo and 200 milligrams. There is a suggestion that these patients were sicker than those in the U.S. trial, because 40 percent were on immunosuppressives. Next.

The efficacy results using an intent to treat show that the SLAM did decrease, but it did not reach statistical significance. There is a significant reduction in flares with 200 milligrams of GL701 and a very significant improvement in the

patient Visual Analog Scale. This is now the third time you have heard this message, Stanford, U.S. study, Taiwan study; and the physician VAS also decreased, although not significantly. Next.

This is an analysis of the time to first flare. Remember that there were fewer flares, but in addition, patients on GL701 took longer to have a flare, P value .044. Next.

To summarize overall the efficacy of GL701 for lupus, for disease activity I have shown you improvement in stabilization in SLE activity, the Stanford study, the U.S. study, the Taiwan study; fewer patients with disease flares: The Stanford study, the U.S. study, the Taiwan study.

In terms of the domain of damage, I have shown you sustained reduction of corticosteroids, and I have also shown you this fascinating data on improvement in bone mineral density in the corticosteroid treated patients.

In terms of what matters most to our patients, quality of life, I have shown you improvement in patient visual analog scales in the Stanford study, in the U.S. study, and in the Taiwan study. Next.

I would now like to introduce to you Dr.

Frank Hurley, who will be leading the statistical discussion.

DR. HURLEY: Good morning, Mr. Chairman, panel members. I would like to take a couple of minutes to discuss briefly some statistical issues.

The first is to consider the strategy of new drug development in uncharted territory. As you have heard this morning, that is how we best describe RCTs and SLE; also, the consideration of the target population, looking at predefined subgroup analysis based on SLEDAI greater than 2; the measurement tolerance for definition of stabilization of disease; differential outcomes for the two primary endpoints for the study GL94-01; and then a discussion of the all randomized ITT versus the modified ITT versus the per-protocol analysis.

As you have heard this morning, there is no FDA guidance document available for study of SLE, and there are very few RCTs published in the literature. This indicates a need for flexibility in the design and analysis of clinical trials in such a situation.

The flexible approach with careful planning, proper execution and scientific rigor certainly does not compromise scientific validity.

One important point is the target population, SLEDAI greater than 2 -- that is, patients with active disease -- was based on GL94-01 and implemented in an amendment in GL95-02.

So we are basically using the information from the first study to affect and modify the how the second study was conducted.

In the per-protocol population, we are minimizing the noise and maximizing the ability to detect treatment differences, a strategy needed when there is no prior knowledge of treatment effect using an instrument or responder analysis with unknown properties in RCTs.

In an ITT population, that is preferred when you have knowledge of the treatment effect in the target population, and also the measurement instrument sensitivity, which allows sample size calculations in adequate statistical power.

In consideration of the target population, the predefined subgroup analysis based on SLEDAI greater than 2, the baseline -- As Dr. Petri mentioned, there was considerable discussion prior to the study and at the investigators meeting, in fact, about excluding patients with low SLEDAI scores, although the original protocol had targeted the SLAM

as the exclusion criteria.

Based on that, prior to unblinding the study there was an analysis of the results looking at -- based on blinded data, looking at the aggregated results to see what the effect of the low SLEDAI scores was. That identified a clinically important subgroup of SLEDAI greater than 2.

In fact, when yo look at the results of that study, you can see that the prednisone target reduction was achieved in two-thirds of the subjects with a baseline SLEDAI less than 2, regardless of treatment group, indicating, obviously, that these patients were quite easy to taper their prednisone dose.

Analysis of the GL94-01 shows a significant difference in the subgroups. If you look at the placebo group, in the SLEDAI less or equal to 2, 68 percent of the patients were responders compared to the SLEDAI greater than 2 group, where only 29 percent of the patients were responders. That is, they were able to taper their prednisone dose. This is a highly statistically significant finding.

Importantly, the SLEDAI greater than 2, based on this, was defined in the final protocol for GL95-02 as an inclusion criterion. That is, it was

designated as the target population in the final protocol for GL95-02, and that was by amendment following the analysis of the earlier trial.

The appropriateness of this target population definition was confirmed in the analysis of GL95-02.

When we turn to the issue of allowing some tolerance in the definition for stability of disease, as has been noted, all of the scales used to assess efficacy in GL95-02 have inherent intra-patient, intra-rater variability. That is, the test-retest variability.

Certainly, the definition of stabilization should include reasonable tolerance to inherent measurement variability. As an example, in the ACR20 for improvement in rheumatoid arthritis, you are looking only at a requirement for five out of seven measures to improve.

Certainly, when we are requiring all four measures to not deteriorate or show improvement, there should be some allowance for the inherent variability of the measures.

Importantly -- and I think that this is critically important to remember -- the tolerance window concept was discussed early during the study,

and basically, the proposal was finalized prior to breaking the blind. So all of this was done on a blinded basis to the results.

If we look at the window, as Dr. Petri defined earlier, the window that was finalized and used by the company in analysis was specified on the basis of the individual scales. The FDA has done a sensitivity analysis looking at the sensitivity of the results to varying size windows.

What they looked at was, if you take a fixed percentage tolerance or variability window on the weighted average of the results, you're looking at a requirement of no tolerance or zero change -- in other words, the follow-up scores had to be exactly the same or better improved over the baseline results compared to allowing some tolerance, some window of tolerance in the results.

Basically, you find over here, this requires all four measures for the patients to have improved in order for the patients to be called stabilized. Obviously, over here as you get down, you say you will allow a tolerance of 40 percent, clearly, just about everybody starts to become a responder then. In fact, what you will see is this right here is the area where the company's measures would come

out on a weighted average basis, just around the ten percent range.

So the robustness of the pre-defined window was assessed using this percent of baseline score on a per-patient basis, and the conclusion, if you look at that analysis, is that the results are significant if you use any window from three to 30 percent.

I would also like to note, as you look at that in terms of the placebo response, in my experience and as you look at the literature, placebo responses in mild to moderate disease, particularly rheumatologic diseases, when you have significant background therapy, it's not uncommon to see placebo responses of 30 to 45 percent.

One of the questions that the FDA has posed is to consider the differential outcome for the two primary endpoints in the 94-01 study. Just briefly to remind you of the two endpoints -- it's hard for me to say two primary endpoints. It sounds like an oxymoron, but it does reflect some of the uncertainty that went into the questions of design of these studies in the early Nineties.

The first primary endpoint was the responder analysis, as Dr. Petri has described for

you, which required sustained reduction of doses to less or equal to 7.5 milligrams a day, including the last visit.

As Dr. Johnson indicated earlier, this was known as the Subpart E endpoint that would be important in terms of an NDA.

The second endpoint was the percent decrease in prednisone dose at the last visit compared to baseline.

The responder endpoint is based -- as Dr. Petri mentioned, is based on a down titration algorithm of dose to the pre-specified lower limit. I'll speak in a minute about the other side of that and sort of the no-algorithm for the dose increases.

For the target population, as Dr. Petri showed you, there was a responder rate of 51 percent in the active compared to 29 percent in the placebo with a P value of .031.

When you look at the percentage reduction in dose, it turns out that that is highly influenced by a large percentage dose increase in a small number of patients. As Dr. Petri mentioned, the increase of dose was not regulated by any algorithm.

If you look at the results for the study on the overall population at the last visit, 30

percent -- there was a 30 percent average reduction for the active group compared to 35 percent average reduction for the placebo group. When you look at the details of that, in seven patients the dose increase was between 100 and 300 percent of baseline.

If we exclude those data points, two of those seven patients were placebo patients. Five of them were in the active group. If you exclude those data points from the analysis, then you find that the average reduction is 48 percent for the active versus 41 percent for the placebo.

I'm not trying to imply that those are the results you should look at, but I think, more importantly, what that shows is the effect of using average reduction as an endpoint, and particularly when you look at average percent reduction, that exacerbates or exaggerates the issue of the outliers.

If we look at one of the other sensitivity analyses that we've done, and you look at the ITT subset using SLEDAI greater than 2 using the window as the company has defined, if you exclude -- or if you say the patients who had no baseline -- no post-baseline assessment but reported deterioration or were discontinued early due to lack of efficacy, if you reclassify those patients as non-responders, you find

that the results are still significant, showing a 58 percent response rate for the active versus 43 percent for placebo.

Considering the all randomized ITT versus the other populations, in the all randomized ITT patients without post-baseline measurements were considered as nonresponders. This means patients that didn't have any treatment and were missing all post-baseline measures and no evidence of clinical deterioration were considered nonresponders.

To address this issue, frequently and quite commonly, people use a modified ITT, which is excluding all patients that don't have any post-baseline assessment and no known clinical deterioration.

I would want to note that the per-protocol population that the company defined is very similar to the modified ITT. The per-protocol population excludes only three more patients, two for less than 60 days of treatment and one for a major protocol violation.

Obviously, the results for the modified ITT, given that there are only three patients different, the results for the modified ITT and the per-protocol analysis are closely similar. In

reviewing the data, as Dr. Petri has shown you, there is no apparent bias observed using either population, and the excluded patients do not appear to be non-random. Thus, the test for the null-hypothesis remains valid.

In conclusion, for the target population with SLEDAI greater than 2 using the defined window for stabilization, all of the analyses show highly significant responder rates for the GL701 200 milligram dose compared to placebo.

Now as a statistician, what I would have to say is that the definition of the target population of SLEDAI greater than 2 is something -- a matter of clinical judgment, as is the use of a tolerance window to define stabilization of patients. So I believe these are matters of clinical judgment, not of statistical principle. Thank you.

Dr. Petri will now continue with the safety discussion.

DR. PETRI: Thank you. Next. The safety data I am going to present to you will include a discussion of deaths, serious adverse events, pooled adverse events, and withdrawals, not just from the two clinical trials I have already discussed with you but also from the open label safety studies.

We will also be discussing hormone changes and breast cancers, and finally, changes in laboratory tests. Next.

There is substantial exposure to GL701. 138 patients have taken it for greater than or equal to 18 months. Next.

If we look at all reported deaths int he GL701 group, there were eight deaths in 495 patients. Next.

If we look at the reported deaths in the placebo patients, there were six deaths in 77 patients. Next.

Serious adverse events were frequent, as we all expect in lupus trials, but very few of them were reported as possibly related to drug. Next.

Withdrawals due to medically serious adverse events did occur with both drug and placebo, but there is no apparent pattern. Next.

There were more premature withdrawals with GL701 due to androgenic complaints, defined as acne and hirsutism. Next.

But as you can see in this table of adverse events with a frequency of greater to or equal to ten percent, many more patients had acne and hirsutism and did not drop out. This is an important

issue that you are going to discuss this afternoon.

If a patient dropped out because of acne or hirsutism, does that void the efficacy of the drug? My response is no, because what would we do if we stopped prednisone in everybody who developed acne? We can treat acne and, as you can see, many patients felt that they could continue in the trial without difficulty.

So acne and hirsutism are more common with GL701 200 milligram dose. Myalgias are less frequent. Next.

This is a table of selected adverse events whose frequency is less than ten percent. They were selected because of an absolute difference of three percent or because there was a statistically significant difference.

There was an increase in reported hypertension AEs in the GL701 patients. However, careful analysis of the actual blood pressures does not reveal any difference. There were more reported AEs for hematuria and creatinine increase. I will be discussing all renal safety issues in great detail.

There were fewer of the following with GL701: Nasal ulcers, joint disorders, lupus rashes, and anorexia. Next.

As one would expect, given the known metabolism of DHEA, both pre and post-menopausal women on GL701 have a significant increase in their testosterone levels. Next.

There is no change in estradiol levels in pre-menopausal women. Next.

In post-menopausal women who are not on hormone replacement therapy GL701 significantly increases their estradiol levels to those that one would expect with low dose hormone replacement therapy. Now please keep this slide in your mind as we now turn to the next slide.

Post-menopausal women on hormone replacement therapy at baseline have actually higher levels of estradiol than those we achieved with GL701 and, as you can see, these women do not have a significant increase when taking GL701. Next.

Four patients developed breast cancer, three on GL701, two of whom were off study, and one on placebo. I wanted to mention, too, that there were two other cancers in the placebo group. Next.

There is no difference in breast cancer incidence -- this is an analysis done in March 2000 -- between GL701 and placebo patients. Most importantly, Genelabs contacted each investigator site this month

to ask if there were any additional reports of hormonally driven cancers. There was one such report, a vaginal cancer that occurred in the placebo group. Next.

What are the implications of these findings on the effects of hormones? First of all, testosterone levels are increased, but the androgenic effects observed were mild, acne and hirsutism, and most patients with acne and hirsutism remained in the trial.

There were no major androgenic effects seen such as virilization or deepening of the voice. Estradiol levels do increase in post-menopausal women not on hormone replacement therapy. Those increases that I showed you are consistent with those seen with low dose hormone replacement therapy.

There was no increase in the incidence of breast carcinoma, no significant increase in vaginal bleeding, and no endometrial hyperplasia was observed in a substudy that is described in your document.

The most important implication is, of course, the increase in bone mineral density that I showed you as an efficacy result. Next.

In terms of routine clinical laboratories, there were no significant effects on the complete

blood count, liver function tests, most importantly BUN and creatinine, and routine serum chemistries. Next.

We know that both DHEA and testosterone affect lipids in normals. So it's not surprising that we found that GL701 reduces the total cholesterol, the HDL cholesterol and the total triglycerides. Next.

When a patient starts Gl701, the HDL cholesterol drops by the three-month visit, and then remains stable. When a placebo patient crosses over, her HDL cholesterol falls at three months but then remains stable. Next.

What are the possible mechanisms for this decrease in HDL and triglycerides? Now, obviously, for a lupus patient a fall in total cholesterol and triglycerides is good news, but lupus patients are at increased risk for atherosclerosis. So is there a concern about a fallen HDL?

Well, testosterone increases hepatic lipase activity, and increased hepatic lipase activity will enhance HDL clearance and possibly affect reverse cholesterol transport, meaning removal of cholesterol from tissues.

So this isn't necessarily bad. In fact, experimental evidence suggests an increase in hepatic

lipase activity might actually be anti-atherogenic. In rabbit studies with DHEA there is an indication of anti-atherogenic effects, but the mechanism is not known. Next.

I am going to show you some really fascinating data on serum complement. Next.

Now in new data from a previous PK study in normals, we can now report that in normal women GL701 reduces C3 complement and also reduces C4. You can see here a mean reduction of -2.3 percent. These are the individual patients in this PK study. Next.

This slide allows you to compare the reductions seen in normals with the reduction that we saw in the SLE patients in these trials. So here's the normals, and here are the GL701 patients at one month and two months.

You can see that this is really quite comparable. This is a physiologic effect of this drug. It reduces C3 and C4 in normals and in lupus patients. Next.

Because there is a reduction, some lupus patients actually shifted from having a normal level of C3 to a low level by their last visit. This occurred in 15.5 percent of the GL701 patients and 5.8 percent in the placebo. Next.

We would like to show you the clinical course of those patients who had this shift from a normal level of C3 to a low level. In the 14 placebo patients two had isolated new onset hematuria. In 36 GL701 patients, three had isolated new onset hematuria, nothing else.

Two had isolated increased proteinuria. You see that both of these patients started out with substantial proteinuria. Two had an increase in serum creatinine. These are both patients who started out with renal insufficiency.

So there are no patients with two events. None of these patients received immunosuppressive therapy for renal lupus flare. Next. Why does GL701 reduce complement in normals and in lupus patients? Well, since it happens in normals, the mechanism is most likely decreased production rather than increased consumption.

DHEA decreases Interleukin-6 production, which may mediate hepatic complement synthesis. DHEA may decrease hepatic production of some proteins, including complement. There is a very interesting study in Klinefelter's showing that testosterone therapy decreases serum complement in Klinefelter's but without any subsequent autoimmune manifestations.

So we consider the decline in complement simply a physiologic effect of GL701. Next.

So the implications are that this decrease in C, which is physiologic, does not correlate with increased disease activity and does not appear to be associated with any worsening renal disease. Next.

I promised that I would look at all of the renal safety data very carefully with you, and I am going to start out with individual laboratory tests. So let's first look at hematuria as an adverse event.

This occurred nine times in the 200 milligram dose of GL701 and one time in the placebo. I want to track through these with you. Many of these should be discounted, because the hematuria was due to menses or a urinary tract infection.

Some of these should be discounted because the hematuria was within the normal range. In two patients, though there was hematuria, there were absolutely no other renal changes to suggest that the hematuria was a renal source.

Finally, you are left with these two patients, one on 100 milligrams and one at 200 milligrams, who had hematuria along with other changes that suggested renal lupus.

These very small numbers -- there does not

appear to be any safety signal here. Next.

Secondly, let's look at creatinine increases. The creatinine increase of greater or equal to .3 milligrams per deciliter occurred in four patients on placebo, three on 100 milligrams and six on 200 milligrams.

If we ask in which of those patients was there something worrisome like new hematuria, proteinuria or immunosuppressive therapy, two patients on placebo, two on 200 milligrams, and this is balanced, doesn't appear to be any safety concern here. Next.

The proteinuria is the most difficult because, obviously, we don't have standard definitions of what is worsening. So we looked at what we thought you would agree were clinically meaningful increases in the 24-hour urine protein at the last visit.

So let's look at patients who actually had proteinuria at baseline, and we will define an increase. If the baseline was greater than 1,000, they had to approximately double, or if the baseline was less than 1,000, they had to have a 500 milligram increase.

That 500 milligram increase is what is defined in the SLEDAI instrument. So I think that's

really quite well accepted. So this occurred in seven patients on placebo, six on 100 milligrams, and 11 on 200 milligrams. But again, let's ask is anything clinically worrisome happening in those patients, a significant renal adverse event, increase in creatinine or new immunosuppressive therapy.

That occurred in four on the placebo, six on the 200 milligram dose. Again, it appears to be very well balanced.

Now let's look at those patients who did not have proteinuria at baseline and define worsening as an increase in 500 milligrams, again this SLEDAI definition. This occurred in one on the placebo and none on GL701.

So again in this analysis, there does not appear to b any renal safety issues. Next.

Now I did another analysis looking at patients who were normal at baseline but doubled protein for at least two visits during the study, but then what I looked at was how were they doing at the last visit. So this is 23 GL701 patients and 14 on placebo.

By the last visit, seven of the GL701 patients were back to normal, as were two of the placebos. So let's now look at the others. Eleven

GL701 patients and eight placebo patients at the last visit had mild proteinuria, less than 300 milligrams a day. Five of the GL701 and four of the placebo had modest proteinuria, 300 to 1000.

Let's look at the actual levels. You see that none get above 450. This really is modest, and nobody had moderate proteinuria. So if you add up here, there are four more patients on GL701 that had mild or modest proteinuria versus placebo. Next.

Now we wanted to combine these analyses into something clinically meaningful. So we want to look at renal flares, but approaching it in many different ways.

This is an analysis that Dr. Strand did based on the patients identified by Dr. Johnson in his medical review. Those are patients who had any two abnormalities. We, though, counted C3 and/or C4 changes one.

What Dr. Strand did was go through the records, look at who had a decrease in their creatinine clearance, who had an increase in proteinuria, an increase in red blood cells, C3 going to a low value, an actual reported adverse event in the kidney, and then what the conclusions were.

You see here that placebo 100 milligram

and 200 milligram patients in study 94-01. You can see there are a couple more patients here at 200 milligrams, but the key word is a couple, and you don't see lots of patients who have everything happening to them, and you also don't see any association with shifting to a low C3. Next.

For 95-02, doing the analysis the same way, there is an equal number of patients here, and again you see no pattern of shifting to a low C3 causing any renal problems. So in this study, everything appears to be extremely well balanced. Next.

I suggested another analysis of renal flares, defining a renal flare as hematuria greater than 5 Rbcs, urine protein going up 500 milligrams -- remember, these are the SLEDAI descriptors -- the serum creatinine going up, serum complement going down, or DNA doubling.

We asked what patients met two or more of these at anytime during the studies. We didn't even ask that these things happen at the same visit. I want to point out to you that in study 94-01 there's some baseline imbalance, as you see here.

There are more patients with proteinuria in the 100 and 200 milligram group. There are more

patients meeting the criteria of this renal flare in the 100 and 200 milligram group in 94-01.

In 95-02 there is no baseline imbalance, and there is absolute balance in patients meeting this criteria of renal flare. So if there is some sort of renal flare issue going on in 94-01, it is most certainly not confirmed in 95-02. Next.

This is looking again at sighs of renal flare using the FDA algorithm. We basically repeated this algorithm. The only thing we did was to count complement and anti-DNA as one event.

In 94-01, if we look at patients meeting one criterion for a renal signal, you can see that it looks like it's very well balanced. Two criteria for a renal signal, looks like it's very well balanced for patients who start normal at baseline.

For patients who start abnormal at baseline, there are a few more patients with one criterion, 100, 200 milligrams, but for two criteria it is balanced, two in 200, two in placebo.

If we look at 95-02, for patients meeting at least two criteria, balanced two and two. For patients meeting two criteria who started out abnormal at baseline, really balanced two and zero.

So we have looked at renal flares every

possible way we can think of, and we don't find anything to suggest a renal safety issue. Next.

I want to show you another study that Dr. Johnson alluded to in his introduction. Dr. van Vollenhoven actually did a study in which DHEA was administered to severe lupus patients along with other appropriate therapy. Patients were randomized to DHEA or placebo, and an assessment was made at six months about whether they had responded.

The definition of response for renal lupus was that the creatinine clearance had to be stable, a greater than 50 percent reduction in proteinuria, and an inactive urinary sediment.

Looking at responders for the patients who entered because of nephritis, six out of eight on DHEA were responders, and nobody worsened. So this study does not suggest that giving DHEA with patients with lupus nephritis causes any problems. Next.

What are the implications in terms of these detailed renal safety analyses I have shown you? If there is any signal for renal safety in 94-01, it is most definitely not confirmed in 95-02. The reduction in C3 appears to be a marker of reduced hepatic synthesis. There is no concern about it as a renal safety signal.

Androgens may increase renal plasma flow, but they do not cause glomerular hypertension. This may explain those very few patients I showed you who had a mild to modest increase in proteinuria on GL701 without any overt evidence of nephritis.

In Dr. van Vollenhoven's study, DHEA administration to severely ill lupus patients with nephritis led to improvement in six out of eight, with none worsening. Next.

Let's now review an overall safety summary for GL701. The majority of adverse events are androgenic, acne and hirsutism. They led to only a small number of withdrawals. Most patients with acne and hirsutism stayed in the study.

Clinical laboratory changes reflect known hormonal effects, primarily androgenic, the increase in testosterone, the decrease in triglycerides and HDL, and there is an increase in estradiol in post-menopausal women not on hormone replacement therapy.

There is a decrease in C3 that occurs in normals to the same extent as lupus patients, without adverse clinical consequences. There was a modest increase in proteinuria observed in very few GL701 treated patients, but without any signal of renal flares, including any decrease in creatinine

clearance. Next.

I would now like to introduce Dr. Murray Urowitz, who is going to give a clinical perspective.

DR. UROWITZ: Mr. Chairman, ladies and gentlemen, you have heard a lot of data this morning, and thank you for listening.

I know that you realize that the data that's been presented to you is really the culmination of careful work done by many investigators over the past seven years, but let me assure you, it's also been of great interest and under significant scrutiny by a number of lupologists who have not been involved in these studies that you have heard of this morning, because of the intense interest in new therapies for patients with lupus.

I am one of those who have not been involved in the studies, but have followed the results with great interest over the last number of years. So I am really pleased this morning to speak to you for a few moments and give you the overall impression of a clinician/investigator in the field of lupus and tell you a little bit about my thoughts of the studies and where I think this drug fits in the armamentarium of patients with lupus.

The first issue I want to discuss with you

is about the nature of the studies themselves, because I believe that the studies that have, in fact, been carried out have laid new ground for us, and I think that the study designs themselves will serve as the prototype for future studies of medications in this condition.

I want to discuss with you four issues around the studies: First of all, the rationale for each of the studies, and their outcomes, as you realize, were in fact different; the challenges involved in the design itself; the advantages that were derived from the study; and then finally, the important findings, the outcomes from the studies themselves. Next slide.

First the corticosteroid reduction study, the 95-01, looking at the first issues of rationale. There are a large number of patients who are on long term steroids presumably to control disease activity. Some of these patients are, in fact, continuously active, as you heard from Dr. Petri, but there are a significant number of patients who continue to receive steroid over long periods of time without obvious disease activity.

This long term treatment with steroids, even in moderate doses, does contribute to significant

additional damage in this condition. And as you saw in the damage index, steroid induced damage is a major contributor, especially in late lupus.

Well, what were the challenges in this design where we were, in fact, withdrawing steroids from patients with systemic lupus? Forced titration of steroids is, in fact, inherently a difficult issue.

A recent study presented last month at the lupus conference by one of Dr. Liang's fellows, Dr. Michael Corzelius from Germany, who did a survey of rheumatologists around the world asking them how they reduced steroids in patients with lupus, found that there was no set algorithm for reducing steroids. Physicians flew by the seat of their own pants and their own expectations.

So developing an algorithm for forced steroid reduction was an important issue, and may serve us well in the future.

The second challenge in this design was that the efficacy variables which were chosen were expected to remain stable. Now for investigators, we like to see efficacy variables improve, but in this issue -- these are patients who are supposedly controlled on their doses of steroids -- we wanted efficacy to be demonstrated by the variables remaining

stable, not necessarily improving.

The third challenge for us was, when we started, is our assumption was that patients on steroids must, in fact, have active lupus, but in fact, we have seen that this is not always correct, that there are patients who have lupus who are being maintained on steroids who don't have active disease and shouldn't be on steroids.

Well, what's the advantage of doing this study? Well, it addresses a very important practical objective, getting patients off steroids. Both physicians and patients want that outcome.

What did we learn by this design? There are a number of very important issues. The first thing we learned is that the correlation between disease activity and steroid dependency is not uniform.

We learned that there are many patients whose SLEDAI was less than 2 and were probably, therefore, clinically inactive. It was very easy to reduce steroids in those patients. So doing studies on those patients trying to show efficacy with a new agent would be useless.

In the patients whose SLEDAI was greater than 2, there was, of course, more opportunity to show

efficacy, because these patients were, in fact, active. I don't know why it took us so long to appreciate this.

For instance, in rheumatoid arthritis we don't start patients on studies unless they have six active joints. Why should we not have said that patients with lupus, in order to show efficacy, should at least have a SLEDAI of 2, some modicum of active disease?

Then we learned also that the treatment effect was present in those patients receiving the lower doses of steroids or the higher doses of steroids, so that the agent was active despite the level of steroid dose.

Well, what about 95-02? What did we learn in that study? First, let's look again at the study rationale. In this study we had to assume that a large number of patients with systemic lupus over a course of one year flared.

The studies, when they look at all patients with lupus, mild, moderate and severe, are clear and reproduced in many centers that somewhere between 60 and 80 percent of all patients will flare each year when they are being followed in a lupus clinic.

So if we have that as an assumption, our efficacy variable then would be to prevent a flare or to prevent a deterioration in a number of endpoints.

Well, then the next issue was, well, how do we define a meaningful endpoint? What is a responder index in lupus? Let me tell you that there are a number of very committed committees around the world that are dealing with trying to define a meaningful responder index in lupus.

I think that what this company has done is that it has actually gone out on a limb, defined a responder index, in fact, made it a very difficult responder index, stacking the index against newer agents, and have actually used it in this trial.

So that the responder index here required stabilization or improvement in four individual -- five individual outcome measures. So if any one of these measures deteriorated, the patient would be considered a failure.

In defining such a very strict responder index, as I said before, they in fact would make it difficult for a new agent to demonstrate efficacy. In addition, we had to characterize, as I said, to stable disease as a responder index -- as a responder endpoint, because, in fact, we have demonstrated that

patients will flare. So if you keep them from flaring, this is, in fact, the responder endpoint.

You've heard from a number of people now about the window concept. That is, allowing some minor variability in some of these responder indices to account for inherent clinical variability. Those of us who do clinical studies recognize that clinical measures have some small amount of clinical variability, and we have to build that into our measures, and that is what the window concept has done.

So we believe that this is an important new advance, this responder definition, and we hope it will be used in future lupus studies as well. Next slide.

Well, what were the challenges? The challenges in this study were also to identify the patient population that could be treated for over one year. Those of you who treat lupus know that it's very difficult to get a patient to take the same amount of treatment consistently over a one-year period.

So this was a difficult population to identify. They had to have mild to moderate lupus. They had to be on stable doses of steroids, and yet

have some measure of active disease; and we had to convince them to stay in the trial for a one-year period.

It was also suggested by the Advisory Committee that we perhaps perform sensitivity analyses to define as nonresponders some of these patients who withdrew prior to the year, patients who may have withdrawn for a minor adverse effect such as hirsutism or acne but yet had had significant improvement in clinical outcomes. We felt that it was important not to lose the efficacy outcomes in these patients as well. Next slide.

Well, what were the advantages of the study design, this responder index design? First of all, the three major domains that are suggested to be followed in lupus, disease activity, health associated quality of life, and damage were all assessed by this responder index.

In addition, deterioration was defined as an outcome measure. So if a patient deteriorated significantly, they were also deemed to be failures. The innovation here is that in any trial patients are generally evaluated at set times. So they come in, and you evaluate them. But what happened between set evaluations isn't necessarily factored in.

This measure, deterioration, was captured at anytime. So if there was evidence of deterioration between the set analysis, that would be considered a failure as well. So that's an extra advantage of using this very strict outcome measure.

Well, what were the outcomes? Well, the responder index, I think, worked. So I think that was very important. We were also able to use flare, as has been defined by the SALENA study, at any point in the study as an outcome measure.

Furthermore, we confirmed that it was important to use patients who had active disease at outset -- that is, a SLEDAI greater than 2 -- as patients who should be studied with the new agent.

Thus, the two study designs differed. Each had their challenges, and I've tried to outline some of them for you. But in fact, these challenges, I think, were turned into advantages. I think they produce significant results, and I think, more important, they have also pointed the way for future therapeutic studies in patients with lupus.

So finally, where do I see this drug fitting into the armamentarium in the treatment of lupus? Well, first of all, the studies are clear. If we look at our studies, these are patients who have

mild to moderate lupus. The drug seems to be effective in controlling the disease manifestations, and that's as measured by the disease -- the hard disease activity measures such as SLEDAI.

In addition, the drug seems to have a positive impact on health related quality of life. So patient associated outcomes. So this is the patient self-assessment and, as important both for physicians and patients, the ability to withdraw steroids without having significant worsening of the disease. Those are very important patient related quality of life issues.

The benefits in this study, as we tried to show you, were significantly greater than any risks, and Michelle has just spent some time outlining that for you.

We have shown that the benefit is present in all three domains of lupus disease in these patients. We think that there may be some other potential long term benefits, such as the improvement in bone mineral density, as was outlined. There are no immediate risks, and Michelle has gone over that in significant detail for you.

One issue that wasn't highlighted enough, and you have it in your data packages, is the fact

that patients with lupus who are taking antimalarials and GL701 had a greater response than those who were taking GL701 without antimalarials, indicating that there may be some synergism in the use of those two drugs, antimalarials and GL701.

Well, two small issues that I would like to close with. The first has to do with therapy in lupus in general. Let me remind the audience that there has been no new therapy for lupus in more than 25 years. In the past decade there have been three multi-center controlled trials of biologic agents in patients with lupus, all of which have either been terminated because of toxicity or shown to have no efficacy.

At the present time, there is nothing on the horizon for the treatment of patients with lupus under investigation. The excitement that was about a few years ago when the new biologics were being tested has been dampened significantly.

This drug, I think, has given some patients and physicians hope that there is some potential success for treatment of some patients with lupus.

The final issue is you may all know that DHEA is available currently as a food supplement.

DHEA is being used by patients and is being suggested by physicians to control patients with lupus. The problem is that the standardization required by food supplements is not the same as that for approved therapeutic agents.

Published data recently have demonstrated that the amount of DHEA in the proprietary compounds that are available ranges from zero to 200 percent of what is said to be in the compound.

So that it would be in the best interest of the patients and physicians to have an agent which was an approved therapeutic agent so that, first of all, standardization would be better and, moreover, the long term safety studies that still have to be done and the other studies of synergism with other medications and its role in more severe patients with lupus will also be done.

This will be accomplished if this is an approved therapeutic agent, and both physicians and patients look forward to the day when we can prescribe this medication for the treatment of patients with lupus. Thank you.

ACTING CHAIRMAN HARRIS: I wish to thank the sponsors for their presentation, that that I got. I wish to apologize to everybody. This was not my

morning for coming late.

This is a rather -- very complex study with some very complex issues, and we are at about ten o'clock. So I do want to get a sense of the questions that one wants to asks, because the issue is, if there are many questions, then perhaps we can take a few now and then go over the break. Then in fact, there may be only a few and, you know, we might be able to get through it before the break.

So let me first open to all of you around the committee as to whether or not there are any questions. And remember, lots of these issues are going to be discussed in depth this afternoon. So they are limited to the slides, please.

DR. SILVERMAN: I have a couple of points of clarification, really. We saw some elegant slides from Dr. Petri of individual patients, particularly her third last slide on GL94-01 where they showed a lovely jump in prednisone dose.

I would just ask her, how many patients were there? I mean, it's very nice to show us one patient, but out of the approximately 300 patients, how many did have this very dramatic jump in prednisone dose?

DR. GURWITH: It's a good question.

Obviously, those were selected slides. The number of patients who were nonresponders, which was approximately 60 percent in the placebo, would be patients who had an increase, some of which were as dramatic and then, similarly, the nonresponders approximately 40 percent of the GL701 group would also have the increases.

We can't say that every patient went up quite that high.

DR. PETRI: I think Dr. Hurley also addressed the issue of outliers, the 100 to 300 percent increases that occurred in five of the GL701, I believe, two in the placebo. But in terms of my showing an example, there were several others similarly dramatic.

DR. SILVERMAN; How many?

DR. PETRI: I don't have the exact number, but there were several other dramatic examples. Dr. Strand would like to respond as well.

DR. SILVERMAN: So the maximum, if I understand, could be five in the GL70 and two in the placebo, but that would not have had to occur at the last visit?

DR. PETRI: Those are the ones who are very dramatic.

DR. SILVERMAN: Correct.

DR. PETRI; We have some slides of some other patient examples that can be shown.

DR. SILVERMAN: And similarly, you showed a very dramatic increase in the GL90, again in your second slide, you saw similarly, and again the number of patients I question off these dramatic slides.

DR. GURWITH: Could you clarify which slides you were talking about?

DR. SILVERMAN: It was the -- a number of slides which show these very dramatic increases at the last visit, and also the number of slides with this window where you had this minuscule increase which, without the window, would have showed a lack of efficacy and very dramatic and very appropriate. But how many patients were there also that would not have come in without your window?

DR. GURWITH: I'll show you that in a second. Again, we'll try to get you the exact numbers maybe during the break.

To answer the question about the windows, could you show the slide about the three percent?

DR. SILVERMAN: No, that wasn't my question. My question was the number of patients who would not have met the criteria because of it.

DR. GURWITH: Right. First of all, if you use the window we used, and how many patients would not have met the criteria? That's 67 patients. That would be a long list to show you. So what we have done here is show you the patients who meet the smallest windows.

You remember Dr. Hurley mentioned that, using a per-patient window, you can go down to three percent. Again, this is hard to see, but these are individual patients who improved on all their scores with the exception of the bolded score for different instrument, which is the one that would cause them to be nonresponders, if you don't use the window.

I apologize for -- These are hard to read. But as you can see, some of these are very small. This is the one patient that Michelle pointed out. Here's another patient with a change in KFSS of 0.2. Here is a change in patient VAS of 1.21 with a baseline of 60.

So that's kind of the individual patients. Now could you show the -- We did a summary slide. This is again 67 patients whose status changes. If you look at the range of the differences that caused them to be -- status to change, you can see from the SLEDAI there would be eight patients with a change of

.8 to .5, because that was the top of the window, and this gives the percent differences between the ranges.

For SLAM there's nine patients from a difference of 0.3 to .89. So again, small differences. Patient VAS, .1 to 9.81. Again, remember that this is a scale of zero to 100. Then finally, the KFSS, very small difference at one side, up to .43.

You can see the VAS and the KFSS had the most patients who changed. You might expect that, because those are the instruments which have the most variability. The patient VAS is not anchored. So a patient does not know what she marked on the previous visit.

DR. SILVERMAN; One final quick question, actually, and this addresses -- We saw very elegantly the patient VAS which had a 10 millimeter window. We were very impressed with the data presented by Dr. Petri showing the statistical significant differences in the patient VAS, but as I was looking at her slides, the difference in the patient VAS which was statistically significantly was 5 millimeters, which is well within our window.

Would somebody like to comment on the clinical significance versus the statistical

significance when it's well within a window of 10, our statistical significance?

DR. PETRI: Earl, I had shown you the mean differences in the instruments, the four different instruments, and that's the one where the mean change in the patient VAS looked impressive. When we are talking about windows, we are talking about a per-patient, not a mean.

DR. SILVERMAN: I understand, but still, could you comment on if you think your -- If your window is based on your assumption that the difference is potentially on day to day, how do you reconcile a 5 millimeter difference when you think it's possible intuitively that this could be a day to day variation? I just want a comment on it.

DR. GURWITH: Again, it's hard to compare a mean for the group and an individual variability. But again, as we showed you, even as low as a three percent window, which means three percent of the individual patients' VAS led to a statistically significant result.

In terms of what is clinically significant, you know, for an individual patient, that's hard to know, because this is, you know, how the patient marks it. A ten millimeter or a three

millimeter change is going to vary from patient to patient.

ACTING CHAIRMAN HARRIS: One more comment, and then we'll have to get the bathroom breaks. Thank you.

DR. ELASHOFF: Okay. This should be two quick questions, one about slide 25 which shows median prednisone doses for the three different groups at baseline. It says nonsignificant, which I can see. But what is the P value, especially if a rank test has been done? I'd like to find out what that P value is.

While you are getting that, the second question is on --

DR. PETRI: I'm sorry. If we could take one question at a time. That slide shows for all patients, and there is no statistical significance.

DR. ELASHOFF: Yes, but I would like to know --

DR. PETRI: The actual P value.

DR. ELASHOFF: -- the actual P value.

DR. GURWITH: It's .1-something. I can't remember exactly.

DR. ELASHOFF: Point-one-something. Thank you.

DR. GURWITH: Again, that has -- That may

be based on some outliers, too. But I'm not sure if we did a rank test or not. It still was not significant with the rank test.

DR. ELASHOFF: Well, I assumed not.

Slide 45 where you are defining these deltas, you show a range -- you show all positive changes on all four things between screening and qualifying visits. Is that because somebody has taken the absolute value or did everybody change in the same direction between those two visits?

DR. GURWITH: The purpose of this was to show the variability between two visits where there is no treatment. So that is the absolute value.

DR. ELASHOFF: Okay. So this slide has absolute value.

ACTING CHAIRMAN HARRIS: What I am going to do -- I'm sure there are going to be more questions. So what I'll do is let's call the break now, and then maybe when we re-start, we'll take about ten or 15 minutes to ask some more questions. Thank you.

(Whereupon, the foregoing matter went off the record at 10:27 a.m. and went back on the record at 10:43 a.m.)

ACTING CHAIRMAN HARRIS: Okay. I again

say last call. We can resume. I would like to invite any additional questions with respect to the presentation made by the sponsors this morning.

DR. FIRESTEIN: Thanks. I had a question for clarification. One of the most common side effects was acne and hirsutism and, obviously, that makes blinding very difficult. Were there any differences in the response rates in patients that reported those sorts of side effects compared with those that did not?

DR. GURWITH: We did try to analyze that in terms of would the potential for unblinding by androgenic effects -- can you present the slide?

While we are getting our slide, just to answer Dr. Elashoff's question specifically, the P value for the mean in all patients for prednisone was .178. Then if you use a rank sum test, it's .163.

DR. ELASHOFF: Thank you.

DR. PETRI: I just wanted to say one clinical thing while we are waiting for the slide to come up.

The investigators remained blinded, because we, of course, also see androgenic complaints with prednisone, as you saw in that adverse events slide. There are a lot of patients on prednisone that

reported acne.

DR. GURWITH: It's called androgenic adverse events. What we did was look at responder -- We looked at patients who had either hirsutism or acne, and then looked at the responder rates, first in the placebo group and then in the GL701 group, whether they had androgenic effects or not.

This is the analysis. So it's really best to look at the placebo group, because those patients shouldn't have the treatment effect. But if you look at them, placebo patients who had androgenic effects, acne or hirsutism, probably, as Michelle mentioned, from their steroids, had a 35 percent responder.

If you look at those that didn't have an androgenic effect, 47 percent -- or 48 percent responder rate. So that suggests, if the androgenic effects were making them think that they are on drug and that they should be doing better, you would expect just the opposite, a higher response rate in the placebo patients who had the effect.

If you look at the GL701, you have -- the results are somewhat reversed. You have a 68 percent responder rate in those patients that had androgenic effects versus 51 percent in those that didn't. But this is a confounded analysis, because the drug -- the

pharmacology of the drug, the desired pharmacodynamics include an androgenic effect.

So this is a confounded analysis, but this analysis, the placebo group who shouldn't matter whether they have androgenic effects or not, you can see at least it doesn't suggest that they were unblinded.

DR. FIRESTEIN: In a normal population that's treated with DHEA, do those individuals have improvement in their VAS, if they have androgenic effects, or even without? Who knows?

DR. GURWITH: We've done a 28-day pharmacology study in normals. They didn't develop androgenic effects.

DR. FIRESTEIN: One other last quick question is whether or not the compound is atherogenic in animals. I know it's too soon to say in people.

DR. GURWITH: The only knowledge I know is the rabbit study that was reported where it appeared to be anti-atherogenic.

DR. SCHWARTZ: In fact, there have been four studies now in rabbits. These are cholesterol fed rabbits, and the differences between the DHEA treated group and the placebo were significant in all four studies, anti-atherogenic.

ACTING CHAIRMAN HARRIS: Dr. Klippel?

DR. KLIPPEL: Yes. I have two questions. In 94-01 I'd like to know if the duration of prednisone use is a variable that is important in dose reduction. That is, the longer a person has been on prednisone, is it more difficult or less difficult or is that an irrelevant piece of data?

DR. PETRI: Jack, I'm not sure that we can address that, because the requirement was that there have been an unsuccessful taper or, if not, a stable dose for 12 weeks. So I'm not sure that we actually have data on duration of prednisone before that.

DR. KLIPPEL: So what I was actually trying to get at: Are the groups balanced for duration of steroid use?

DR. PETRI: I don't think that was even captured, Jack. So I don't think we can address that.

DR. KLIPPEL: Okay. I have a second question. In 95-02, as I understand it, approximately half the people were on steroids and half weren't. Did you look at those groups separately in terms of both response and effect on bone mineral density?

DR. GURWITH: The answer is yes to both.

DR. SCHWARTZ: Yes. On the bone mineral density, it was intentionally prospectively set up,

that only patients who had been on corticosteroids for at least six months were to be eligible to have the bone mineral density scans because, obviously, we know how critical this problem is for lupus patients.

So of the 37 patients, all of them were on chronic steroids for at least six months.

DR. KLIPPEL: I was actually -- I was asking: So what happens to bone mineral density for those who aren't on steroids? That is, if you control lupus disease activity, does that, in and of itself, affect bone mineral density?

DR. SCHWARTZ: Well, that's an entirely different study.

DR. KLIPPEL: Okay. So you haven't done that?

DR. SCHWARTZ: No. In this case, the steroids were required to be fixed for the entire year. So this wasn't a taper. So I can't tell you what we would have seen without. However, it is known that lupus patients do have lower bone mineral density, irrespective of steroid use. That has been published, and it's probably inherent to the disease itself as well, because circulating cytokines such as IL-6 are elevated in lupus, and IL-6 is involved with bone resorption.

DR. JOHNSON: Can I add something to Jack's question. Jack, there was an analysis done that accompanied -- we did it jointly, on the response rate in the first study, split out by how you got into that study, whether you did have an unsuccessful taper or whether you were just on stable steroids. Remember those two different ways you were steroid stuck.

It didn't differ much in those arms -- between those two groups.

DR. PETRI; Jack, can I address your question but from a different dataset. From our Hopkins lupus cohort we have looked at predictors of bone mineral density, and prednisone remains the strongest associate, putting everything else in that we know affects osteoporosis, but low C4s are in the model, suggesting that some lupus associated factor is there as well. But prednisone swamps all the others.

DR. GURWITH: Just to answer -- now to answer your other question about corticosteroids and responders, that's on page 68 of our briefing document. Basically, the response rates for GL701 are about the same, regardless of whether patients are on steroids or not, and they don't change that much for placebo either.

DR. TILLEY: I was just wondering if you

knew anything about the quality of this increased bone, because I'm familiar with the fluoride literature where an increase in bone mineral density wasn't necessarily increase in the right kind of bone.

DR. SCHWARTZ: Yes. For the record, I should introduce myself. I'm Ken Schwartz, Senior Medical Director with Genelabs.

Fluoride is an entirely different story. That's where it's becoming incorporated into the matrix and clearly disrupts the matrix. With a drug such as GL701 or DHEA where you are talking about asteroid hormone, which translate at the local level in bone to either local tissue effects of androgenic or estrogenic or both, it's similar to what you would see with HRT.

So while we haven't done bone biopsy studies, there is no reason to suspect that this would be any different from the finding that you -- positive findings that we see with HRT in general on bone long term effects.

I should add, it wasn't pointed out that the changes in bone mineral density that we saw, the positive, were very similar to the alendronate studies in steroid treated patients, almost very similar as far as percentage gain in one year.

DR. ANDERSON: Yes. I'd like to ask --

DR. SCHWARTZ: Oh, okay, here. I can't even see it very well myself. But this is addressing maybe the question about the effects on bone for the patients who were receiving less than or equal to 5 milligrams per day, particularly right on the spine, compared to those who were receiving greater than or equal to 5 milligrams per day.

Do we have a pointer? Again, even on the low dose steroids here in the placebo in the spine, they lost minus two percent compared to the GL701 that gained 1.9, six percent. You know, you are only talking about 20 patients here, but still you have a P value of .06. This is telling you how strong and how physiologic this effect is.

It also points out the risk to your lupus patients, that you think you are treating them with so called low dose steroids, and that is not the fact for bone.

DR. ANDERSON: Yes. I'd like to ask about the nature of the two populations of patients studied in these two studies, because it was so notable that the percentage of the participants who are smokers was considerably higher in the first study than in the second.

There's no information that I could find about where the centers were or how the patients were selected to take part in the studies.

DR. GURWITH: I probably can't answer the question. You are asking why there were more smokers in 94-01 than 95-02.

DR. ANDERSON: Yes, and what other differences there might have been between how these patient populations were assembled.

DR. GURWITH: You know, the centers were chosen to try to find people who -- experienced investigators who have patients with lupus. This is an orphan disease. It's hard to find enough investigators, because we had a fair number of investigators in the site.

So there's a few sites that have, you know, maybe lower socioeconomic groups of patients, but it's the only thing I can think of. Ken wants to answer.

DR. SCHWARTZ: Yes. I'll contribute my two cents. Actually, the centers in the first and second study were identical except for the fact there were more centers in the second study. The first study had 18 centers, because it was only a 191 patient study, but with the magnitude of the second